Huntington's Disease: Movement Disorders and Treatment

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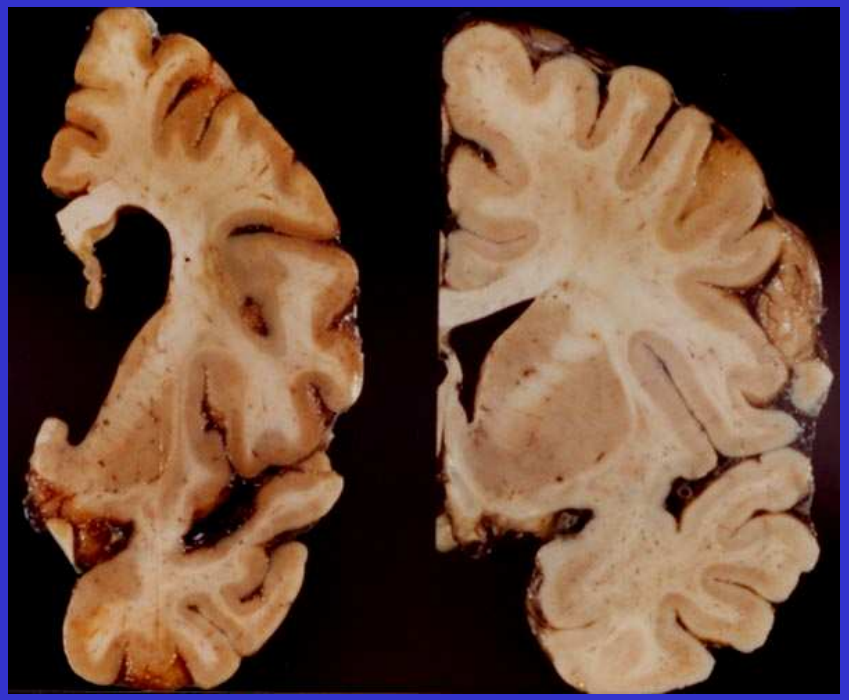
Credits and Conflict of Interest Statement

- Some of the slides and Tetrabenazine (“Xenazine”) info adapted from HSG, FDA, GAHEC, and Creighton University web sites
- No conflicts of interest to declare

Huntington's Disease

- Selective neuronal degeneration in Basal Ganglia--Caudate and putamen, but also cerebral cortex and other regions
- CAG expansion mutation: longer CAG repeats have earlier onset and more widespead degeneration



CAG-CAG-CAG (DNA)

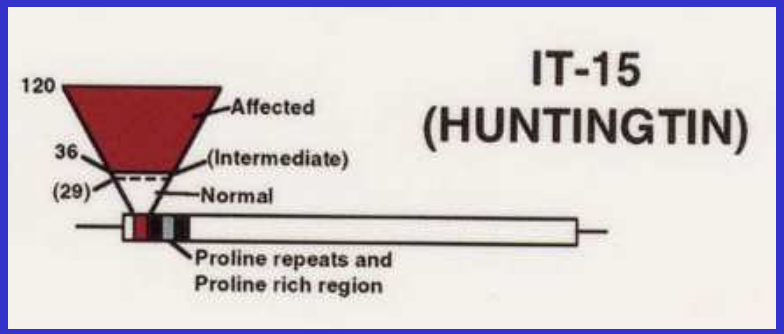
↓

CAG-CAG-CAG (RNA)

↓

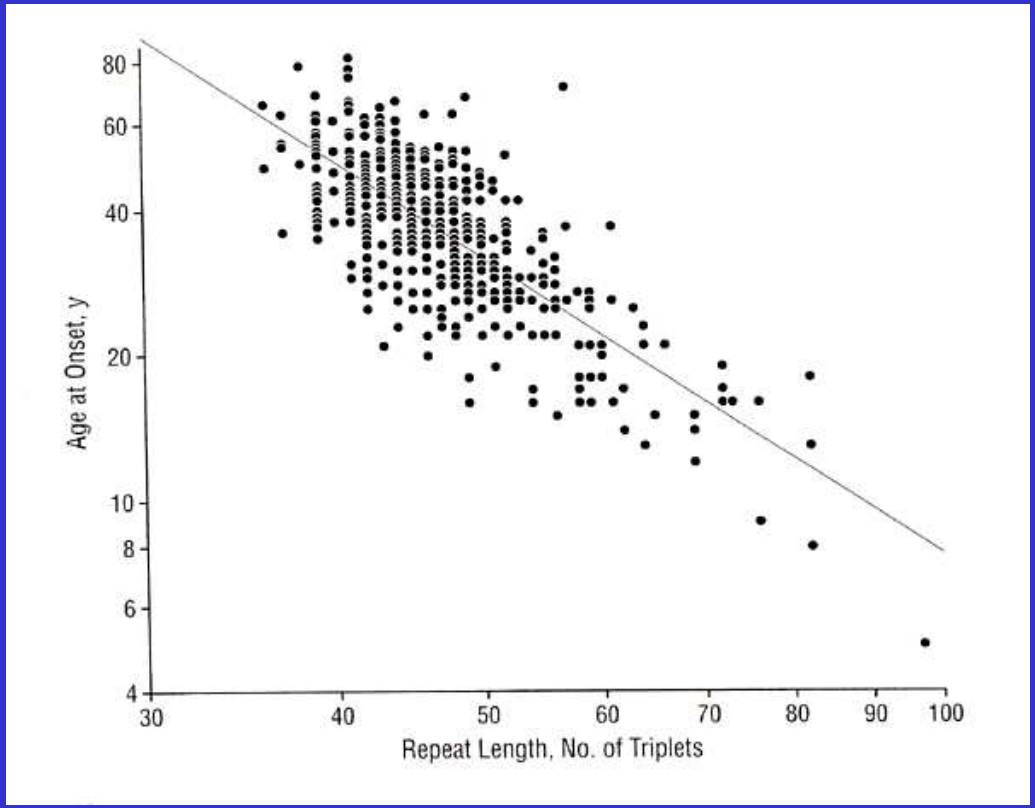
Gln---Gln---Gln (Protein)

(Q) (Q) (Q)



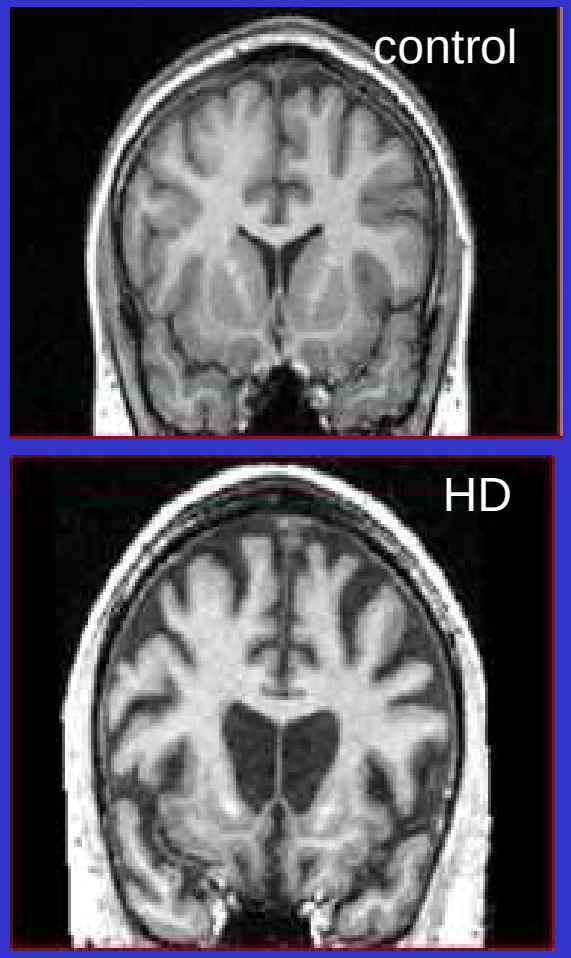
CAG Repeat length and Age of Onset of HD

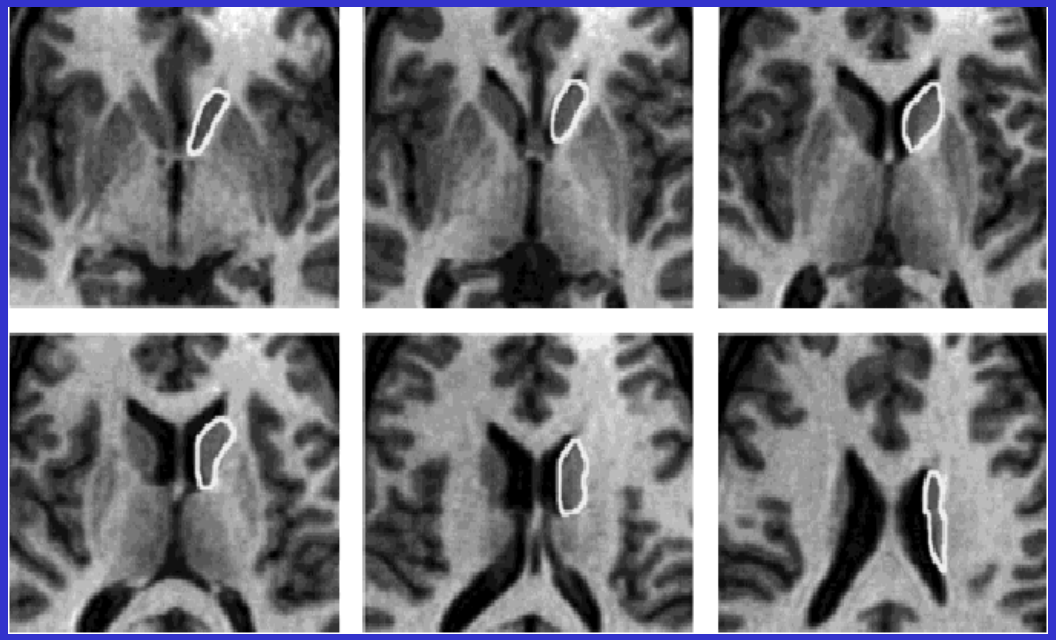
- CAG repeats of 35 or less do not cause HD
- Incomplete penetrance (delayed onset) for CAG 36 to 40
- Longer expansions result in earlier onset ages—thus can roughly predict onset age
- Determinants of the rate of progression are still unknown



--Ranen et al Am. J. Hum. Genet. 1995, and
Margolis et al Arch. Gen. Psychiat. 1999

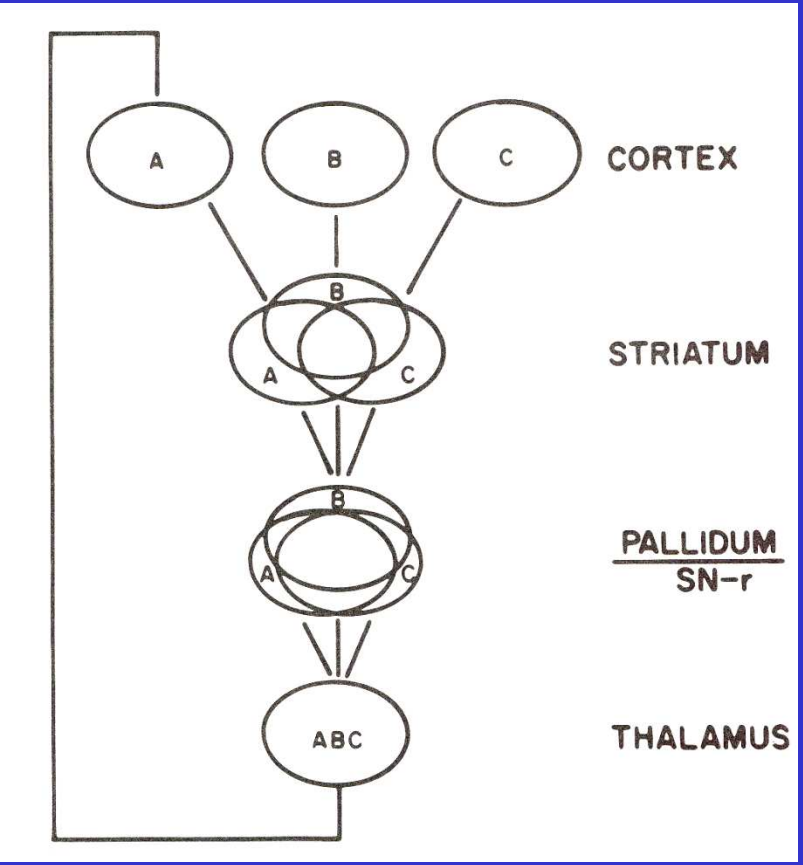
Quantification of Caudate Volumes: Regions of Interest





--Aylward et al Neurology 2004

Simplified Basal Ganglia Circuit



Movement Disorder

- Involuntary movements- eg chorea
  - Often begins with hands or feet
  - May also include noises (“vocal tics”)
- Impaired voluntary movements
  - Clumsiness, swallowing, dysarthria, stiffness, slow movements
  - Eventually eclipses the chorea
  - Also “apraxia” difficulty organizing movements in space

Involuntary Movement Disorders

- Terms—”Hyperkinetic,” “Dyskinetic,” “Bradykinetic”
- Chorea (not really “dance-like”….)
- (Athetosis)
- Tics
- “dance-like” gait
- Dystonia
- Bradykinesia and rigidity

- Course: chorea early, but bradykinesia and rigidity late

Cognitive Disorders

- Disorders of “Executive Function”
  - Losses in speed, attention, and flexibility
  - Orientation, memory, language relatively preserved
- Impaired judgment can be a problem
- Mild early; more pronounced problems later

Types of Psychiatric Disturbances

- Mood disorders
  - Depression and mania
- Obsessive-Compulsive symptoms
- “Personality change”
  - Irritability, apathy, disinhibition

Depression

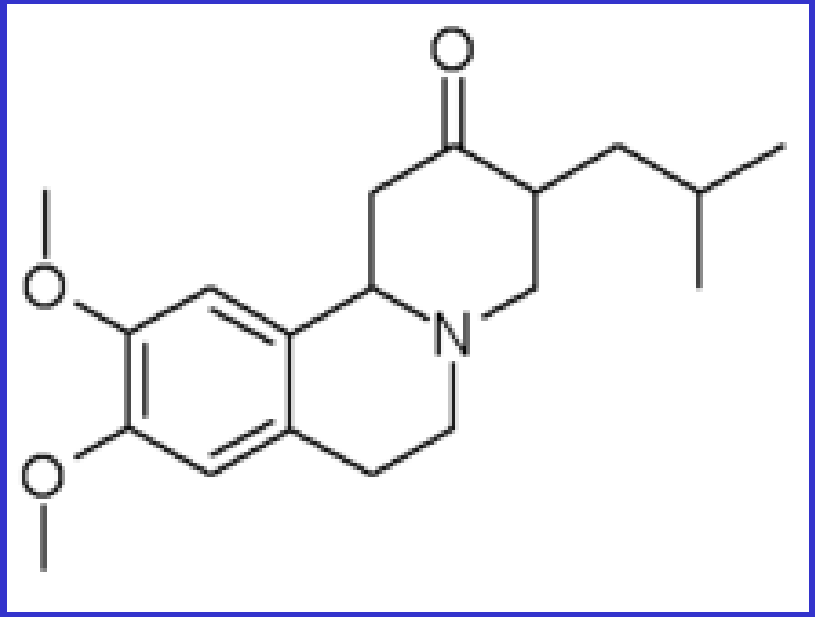
- Sad mood, diminished self-attitude (feeling “helpless and hopeless”), loss of interest in usual activities, poor sleep and appetite etc—suicide is potential complication….
- High prevalence of depression
  - ~40% in HD by some estimates
  - Suicide rate 4-6x higher than normal
- May still be underdiagnosed
- Distinguished from apathy

Xenazine® - Tetrabenazine

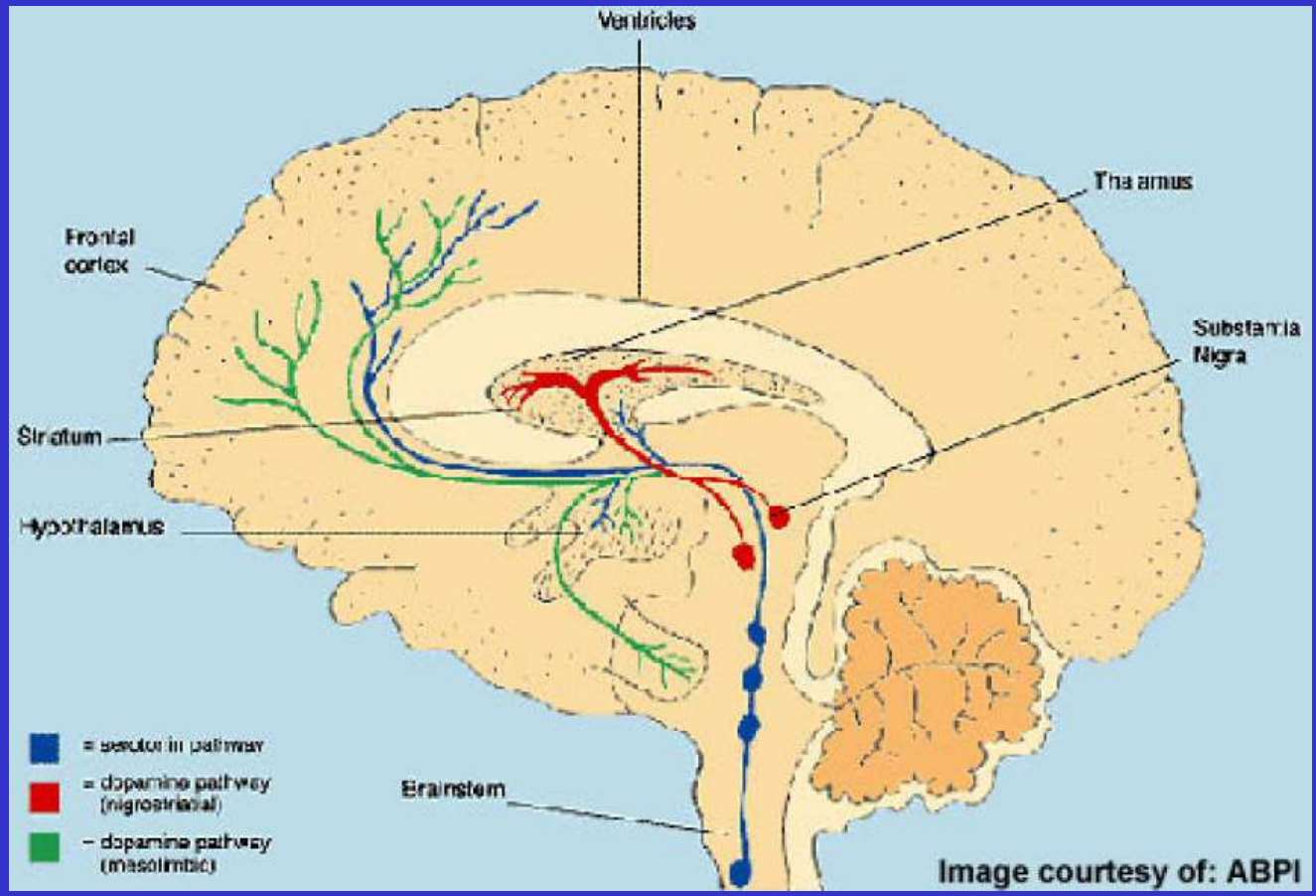
Summary

- Xenazine®, tetrabenazine, is the first medication with a FDA-approved indication for Huntington's disease associated chorea. FDA Approval Date: 08/2008
- Patients must be thoroughly screened for depression and suicidality, as the FDA has issued a black box warning against using tetrabenazine in patients with depression.
- Also, tetrabenazine should not be used in patients taking reserpine, MAOIs, or drugs that prolong the EKG QTc interval.

Xenazine® - Tetrabenazine



Brain Monoamine Pathways



"Tetrabenazine as antichorea therapy in Huntington disease: a randomized controlled trial"

HSG, Neurology. 2006; 66(3): 366-72.

- Objective
  - To examine the safety, efficacy, and dose tolerability of tetrabenazine for treating chorea in Huntington disease (HD)
- Study Design
  - Multicenter, prospective, randomized, double-blind, placebo-controlled dose-finding study
  - 84 randomized → 54 treatment arm; 30 placebo arm
  - Treatment group: Dose was increased by 12.5mg /day per week up to 100mg or until desired antichoreic effect or intolerable SEs occurred
  - Duration: 12 weeks

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- Inclusion Criteria
  - HD as confirmed by the presence of a characteristic movement disorder (chorea), a family history, and an expanded CAG repeat (N > 37)
  - Ambulatory with total functional capacity > 5
  - Total maximum chorea $\geq$ 10
- Exclusion Criteria
  - Disabling depression, dysphagia, or dysarthria
  - Currently taking dopamine-depleting medications, D_2 blockers, dopamine agonists, MAOIs, levodopa,amantadine, or memantine

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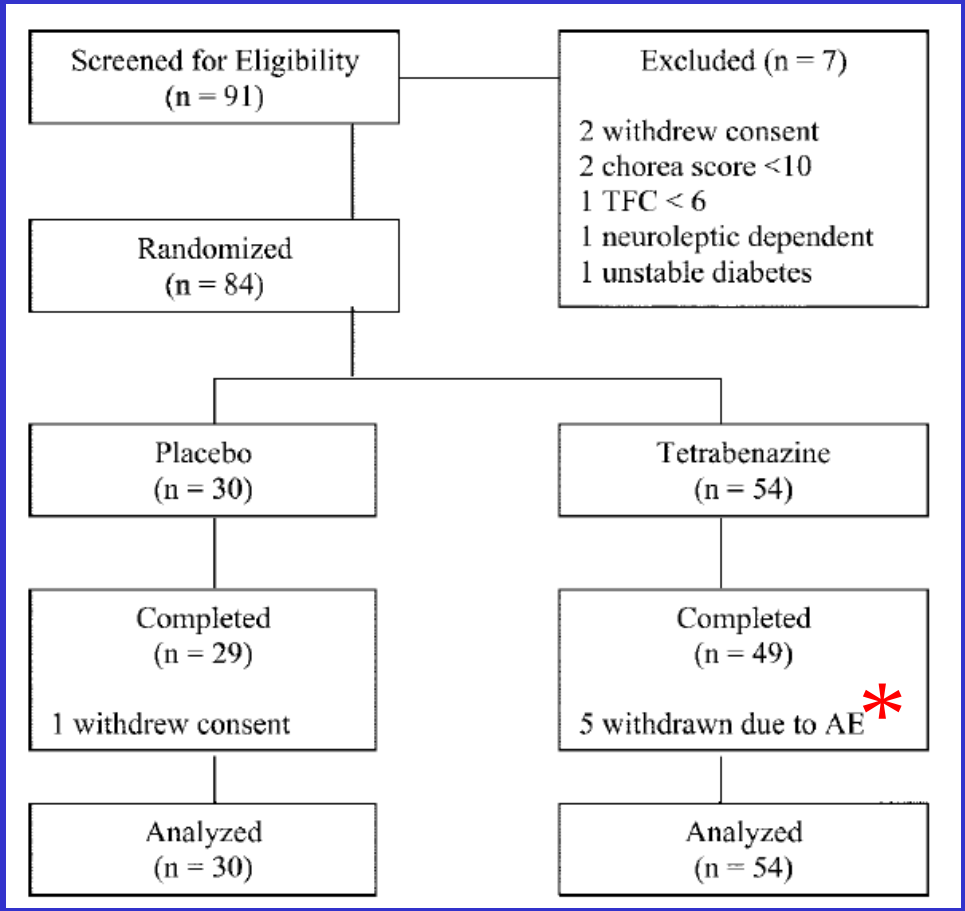

*Note—one "completed" suicide……

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	Direction of favorable change	Placebo, n = 30	TBZ, n = 54	*p* Value < 0.05
Primary outcome variable				
Δ UHDRS tot max. chorea	−	−1.5 ± 0.7	−5.0 ± 0.5	0.0001*
Secondary outcome variables				
CGI Global Improvement‡		3.7 ± 0.2	3.0 ± 0.2	0.007*
Δ UHDRS total motor	−	−3.5 ± 1.5	−6.8 ± 1.1	

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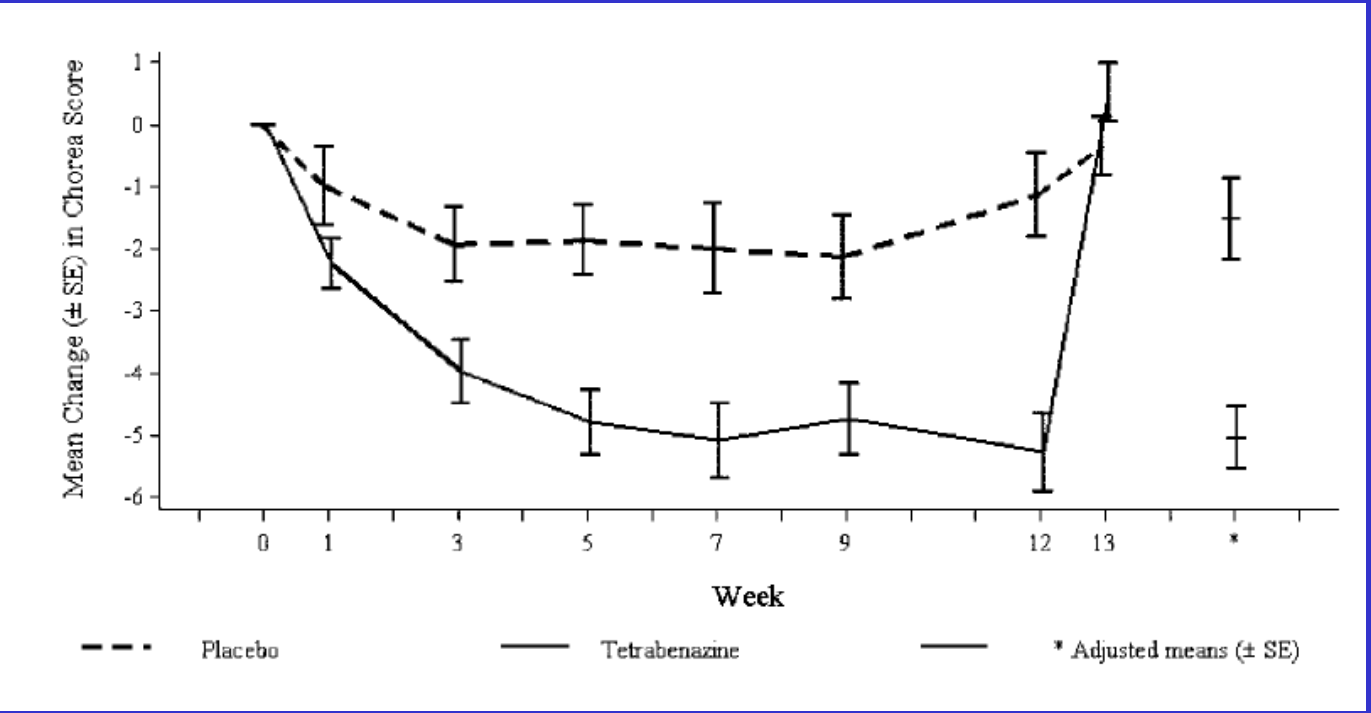

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Table 2 *Tolerability analyses*

Variable	Placebo, n (%), n = 30	TBZ, n (%), n = 54	*p* Value
Subjects withdrawn (see text)	1 (3.3)	5 (9.3)	NS
Subjects experiencing at least one SAE (see text)	0 (0)	4 (7.4)	NS
New AEs per subject, mean ± SD			
All	1.5 ± 1.8	3.8 ± 3.1	0.0005
Excluding mild	0.6 ± 0.9	1.9 ± 2.0	0.0007
Subjects reporting AEs			
All	21 (70.0)	49 (90.7)	0.01
Excluding mild	10 (33.3)	37 (68.5)	0.002
Subjects with week 12 reduced dosage due to intolerability	1 (3.3)	24 (44.4)	<0.0001

TBZ = tetrabenazine; SAE = serious adverse event.

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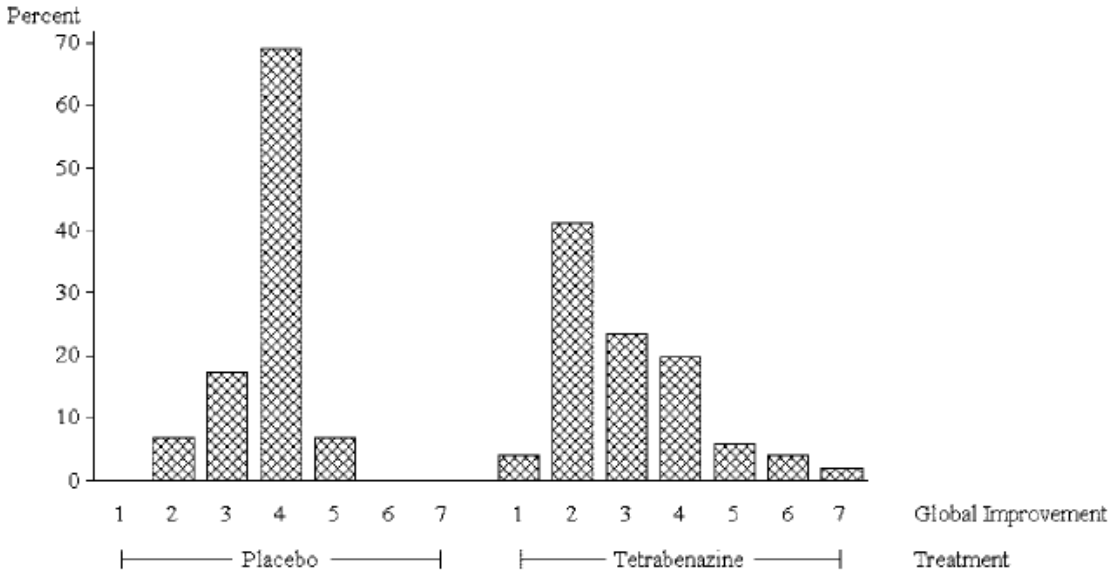

Figure 3. Distribution of Clinical Global Impression Global Improvement ratings at week 12 (end of active treatment phase) by treatment group. Scores are as follows: 1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, 7 = very much worse. There is a shift of the curve to the left (improvement) in the tetrabenazine group ($p = 0.0001$ for proportion achieving score of ≤ 3; χ^2 intention to treat).

Xenazine® - Tetrabenazine

More Common Adverse Effects

Sedation/somnolence	(31%) [3%]
Fatigue	(22%) [13%]
Insomnia	(22%) [0%]
Depression	(19%) [0%]
Akathisia	(19%) [0%]
Nausea	(13%) [7%]

Xenazine® - Tetrabenazine

Contraindications

- "Black Box" warning:
  - Inadequately treated depression and patients who are actively suicidal
- Contraindications and warnings:
  - Hepatic function impairment
  - Concomitant use with MAOIs or reserpine
  - Akathisia
  - CNS depression
  - Esophageal dysmotility/aspiration
  - Neuroleptic Malignant Syndrome
  - Orthostatic Hypotension
  - QT prolongation

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Other Treatment for Chorea

- Dopamine receptor blocking agents
  - Eg haloperidol (“Haldol) and related drugs
- Effective for chorea
- Side effects include sedation, bradykinesia and rigidity (especially in excess)
- Does not cause depression
- Can be helpful for irritability, other emotional symptoms
- Has never been compared to tetrabenazine….

What Potential Benefits to Expect from these Drugs

- Decreased chorea
- MAY help with gait
- Little help for dystonia
- NO benefit for incoordination, slow or stiff moevemnts

- Thus these drugs of most benefit early in the course of HD, less benefit later

- First (symptomatic) treatment for HD….we look for more to come in the future….